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Nickel-Catalyzed Asymmetric Reductive Cross-Coupling to Access 1,1-Diarylalkanes

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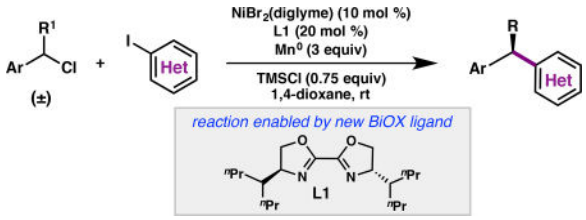
Abstract

An asymmetric Ni-catalyzed reductive cross-coupling of (hetero)aryl iodides and benzylic chlorides has been developed to prepare enantioenriched 1,1-diarylalkanes. As part of these studies, a new chiral bioxazoline ligand, 4-heptyl-BiOX (**L1**), was developed in order to obtain products in synthetically useful yield and enantioselectivity. The reaction tolerates a variety of heterocyclic coupling partners, including pyridines, pyrimidines, indoles, and piperidines.

Graphical abstract



Ni-catalyzed cross-coupling reactions have emerged as powerful methods to forge C(sp^2)–C(sp^3) bonds.[1] Nicatalyzed *reductive* cross-coupling reactions are one subset of these transformations, which couple two organic electrophiles and use a stoichiometric reductant to turn over the Ni catalyst.[2,3,4] Whereas an array of conventional Ni-catalyzed cross-coupling reactions have been rendered highly enantioselective (e.g. Suzuki,[5] Negishi,[6] Kumada[7] reactions),[8] less progress has been made in the development of asymmetric reductive cross-coupling reactions.[9] Given that many of these reactions work well for secondary alkyl substrates and provide chiral products, it would be of value to develop enantioselective variants. In this communication, we report an enantioselective Ni-catalyzed reductive cross-coupling between aryl iodides and secondary benzylic chlorides (Figure 1). This success of this effort hinged on the development of a new chiral bioxazoline (BiOX)

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ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, compound characterization data, ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

ligand, 4-heptyl-BiOX (**L1**), which provides 1,1-diarylalkanes with both improved yield and enantioselectivity relative to previously disclosed BiOX ligands.

A number of commercial pharmaceuticals possess stereogenic 1,1-diarylalkane motifs,[10] and as a result, significant effort has been devoted to the enantioselective synthesis of this substructure. As a complementary approach to methods such as asymmetric hydrogenation[11] and conjugate addition,[12] Ni-catalyzed stereospecific[13] and stereoconvergent[14] cross-coupling reactions have been developed.[1516] For example, in 2013, Fu and coworkers reported the enantioselective Negishi coupling of benzylic mesylates with aryl zinc halides to furnish 1,1-diarylalkane products in good yields and high enantioselectivity.[14a] However, a limited scope of heteroaryl substrates was demonstrated.

Based on our previously disclosed research,[9c] we hypothesized that Ni-catalyzed reductive cross-coupling could provide improved access to heterocycle containing products. However, a challenge in the development of such enantioselective reactions is that as one changes electrophile class (e.g. from vinyl halides to aryl halides), or as one alters the ligand, the product yield and ee can decrease dramatically. Indeed, efforts to prepare enantioenriched diarylalkanes via asymmetric reductive coupling[14b] or Ni/Ir synergistic catalysis[14c] have proved challenging. In 2015, Weix reported a reductive cross-electrophile coupling between primary mesylates and aryl bromides; this report contained a single enantioselective coupling of (1-chloroethyl)benzene with 4-bromoacetophenone, which proceeded in both modest yield and ee.[14b] Similarly, Molander reported that coupling of (1-phenylethyl) potassium trifluoroborate with 4-*t*-butylbromobenzene proceeds in 65% ee, and coupling of more electron deficient arenes occurs with lower enantioselectivity.[14c]

Consistent with the challenges encountered by others, submission of a mixture of (1-chloropropyl)benzene (**1**) and 5-iodo-2-methoxypyridine (**2a**) to the optimal conditions identified for the Ni-catalyzed asymmetric reductive cross-coupling of benzylic chlorides with vinyl bromides provided **3a** in only 12% yield and 10% ee (Scheme 1a).[17] Similarly, use of the conditions developed for the reductive cross-coupling of heteroaryl iodides with α-chloronitriles failed to deliver detectable amounts of **3a** (Scheme 1b).

Despite these discouraging results, we initiated studies focusing on the cross-coupling between **1** and **2a** by screening a variety of chiral bidentate ligands under both sets of conditions shown in Scheme 1. From this study, it was determined that performing the reaction in 1,4-dioxane with ^{i}Pr-BiOX (**L2**) as the ligand and TMSCl as an activator produced **3a** in 22% yield and 68% ee (Table 1, entry 2). We found that both the yield and the enantioselectivity of the reaction could be improved by increasing the length of the BiOX alkyl chain, with 4-heptyl-BiOX (**L1**), delivering **3a** in 84% yield and 90% ee (entry 1). We note that Bn-BiOX (**L5**, entry 5) and serine-derived ligand **L6** (entry 6), the ligands used by used by Weix/Molander and Fu, respectively, perform poorly under the optimal conditions. Control experiments confirmed that no reaction takes place in the absence of Ni, ligand, Mn^0, or TMSCl. Zn^0 and TDAE performed poorly as reductants (entries 7-8).[18] No product was detected when TFA was used as an activator in place of TMSCl (entry 9)[19] and when DMA is used as solvent, the yield and ee both drop substantially (entry 10). Use of aryl bromide **5** instead of **2a** delivered **3a** in only slightly reduced yield and comparable ee

(entry 11), while employing benzylic bromide **6** in place of **1** increased formation of bibenzyl homocoupling product **4** at the expense of **3a**, and the ee of **3a** was slightly lower (entry 12).

With optimized reaction conditions in hand, we evaluated the substrate scope of the aryl iodide coupling partner (Table 2). Pyridyl iodides bearing substitution at the 2-position couple smoothly (**3a–3d, 3f**), as do pyrimidines (**3e, 3g**) and indoles (**3h**). Non-heteroaryl iodides bearing either electronrich (**3j, 3k**) or electron-poor (**3i, 3m–o**) functional groups couple smoothly, although slightly lower ee is observed with more electron-rich arenes. It is notable that acidic protons are tolerated (**3k**); no protodehalogenated byproducts observed. The cross-coupling is orthogonal to aryl triflates and boronates, affording **3o** and **3l** in excellent yields and providing handles for further derivatization. When the reaction was conducted on 2.0 mmol scale, pyridine **3a** was produced in 63% yield and 91% ee.

Next, we turned our attention to the scope of the benzylic chloride coupling partners (Table 3). Substrates with either electron-donating or -withdrawing substituents at the *para* position couple in comparable yields and enantioselectivity (**8a–8d**). In addition, *o*-substitution with either methoxy (**8e**) or fluorine (**8f**) is tolerated, although the products are formed in decreased yields. Substituents of varying steric encumbrance can be incorporated at the α-position of the benzylic halide (**8g–8m**). Of particular interest, good chemoselectivity is observed for coupling of the benzylic chloride in preference to the primary chloride (**8h**). *N*-Bocpiperidine (**8l**) and dibenzofuran (**8m**) groups are also tolerated, providing the products in serviceable yields and excellent ee.

To demonstrate the synthetic utility of our method, we synthesized diarylalkane **11**, an intermediate in the synthesis of the commercial anti-depressant sertraline (Scheme 2a).[20] Cross-coupling of 1-chloro-1,2,3,4-tetrahydronaphthalene (**9**) with commercially available iodobenzene **10** provides chiral tetrahydronaphthalene (**11**) in 70% yield, and 84% ee. Benzylic oxidation of **11** using 3 equiv of CrO_3 in $AcOH/H_2O$[21] afforded tetralone **12** in 51% yield (unoptimized) with no erosion of ee.[22] Tetralone **12** is a known intermediate in the synthesis of sertraline.[23]

To probe for the intermediacy of radical species, the reaction was conducted in the presence of TEMPO.[24] No significant decrease in yield was observed, and no TEMPO trapping adducts were detected. When cyclopropyl chloride **14** was subjected to the standard cross-coupling conditions, alkene **15** was obtained in 57% yield (Scheme 2b).[25,26] These findings are consistent with a mechanism that proceeds through a non-persistent alkyl radical, however we cannot rule out the possibility of a Ni-mediated cyclopropane opening pathway. Further studies of the mechanism are ongoing; it is unclear at this time whether the absolute stereochemistry is set during the oxidative addition or reductive elimination steps.[14c]

In conclusion, we have developed a Ni-catalyzed asymmetric reductive cross-coupling between (hetero)aryl iodides and benzylic chlorides. This transformation enables the synthesis of enantioenriched 1,1-diarylalkanes from simple organic halide starting materials. These efforts resulted in the discovery of a new chiral BiOX ligand, 4-heptyl-BiOX, which

we expect will find application in other transition metalcatalyzed cross-coupling processes.[27]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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24. A control experiment in which TEMPO was treated with Mn^0 and TMSCl in dioxane indicated that TEMPO is stable under the reaction conditions however we cannot rule out the possibility that reduction of TEMPO precludes trapping.
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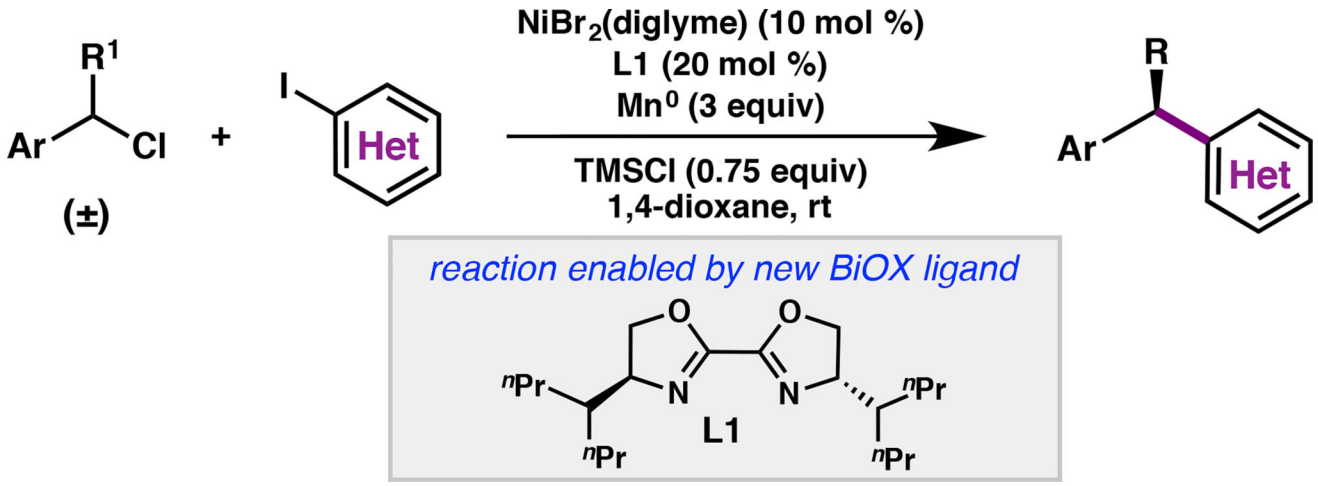
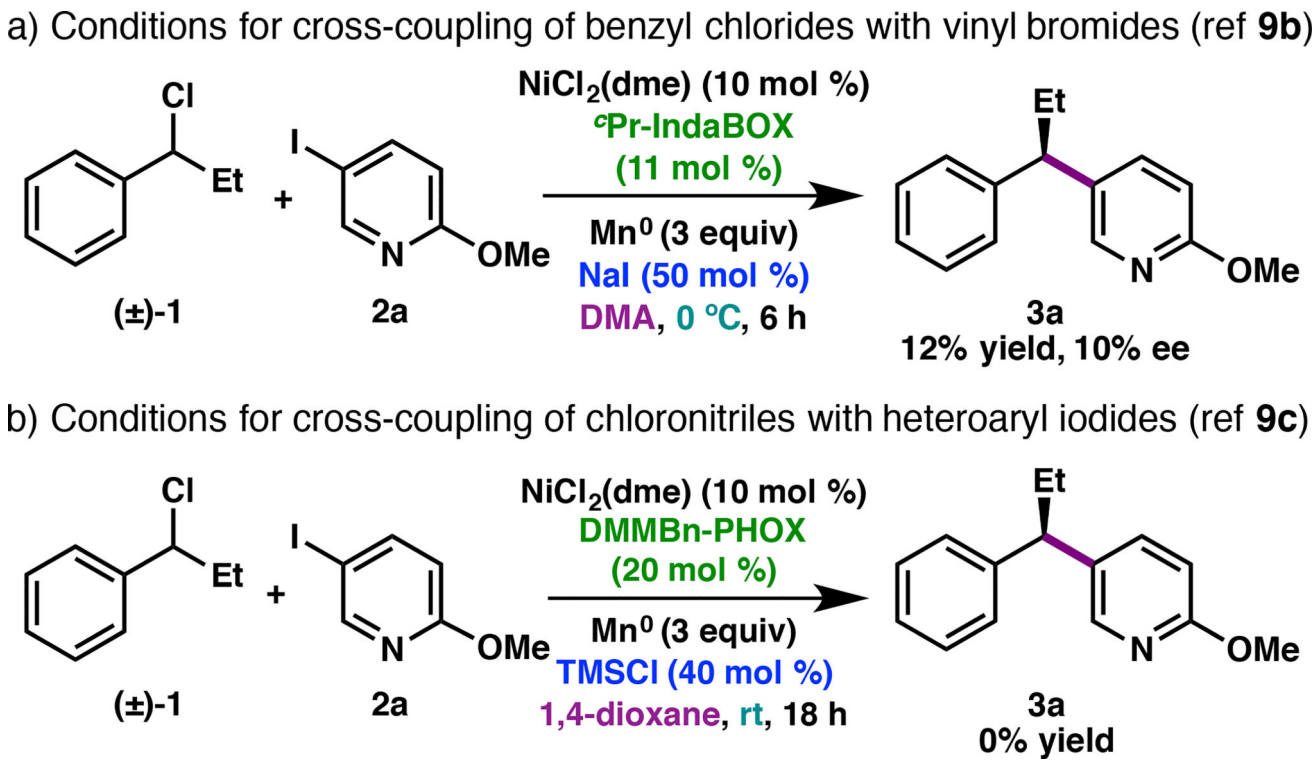
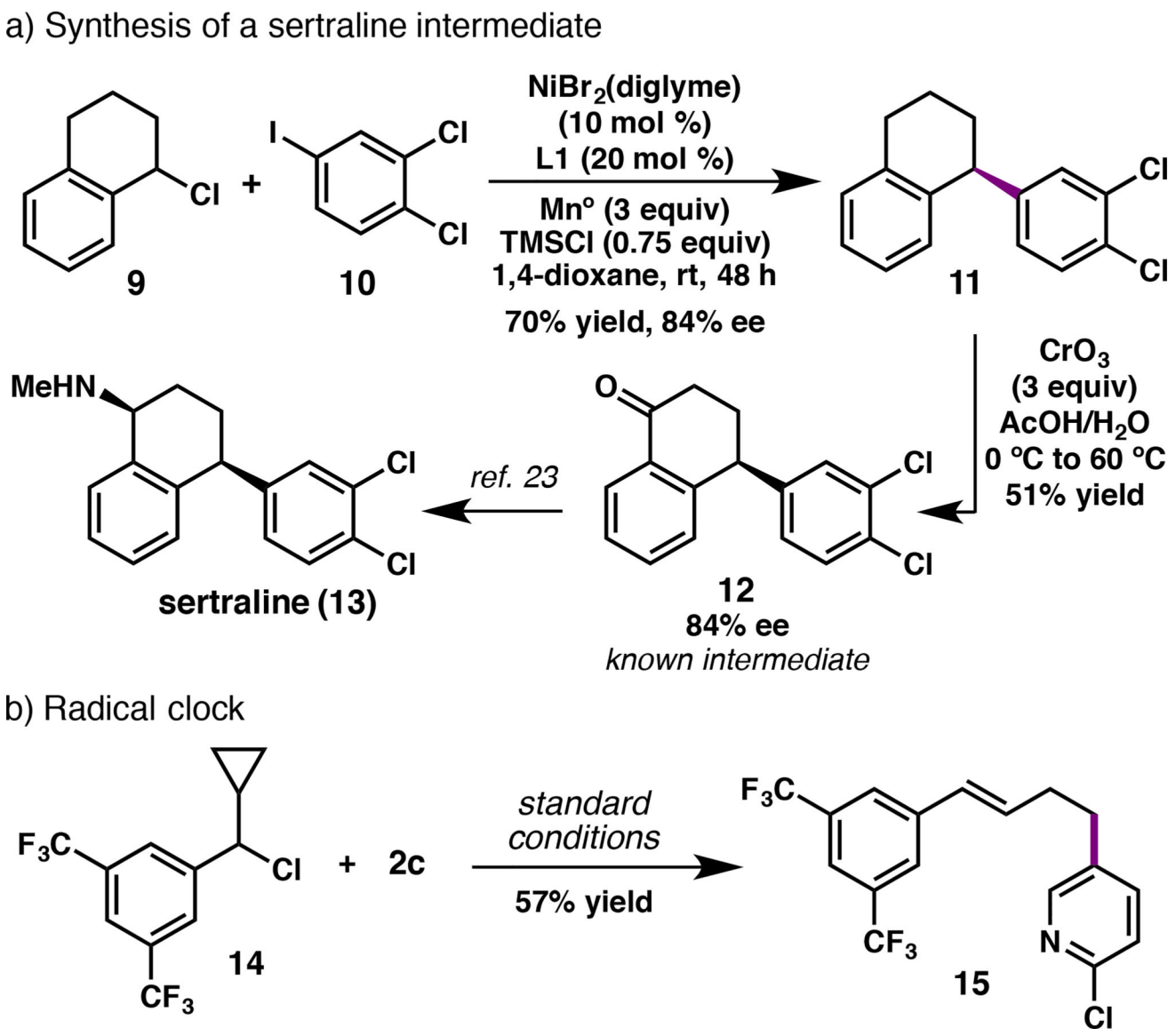


Figure 1.
Ni-catalyzed enantioselective reductive cross-coupling to prepare diarylalkanes.



Scheme 1.

Application of previously developed cross-coupling conditions to the coupling between **1** and **2a**.



Scheme 2.
Synthetic applications and mechanistic experiments.

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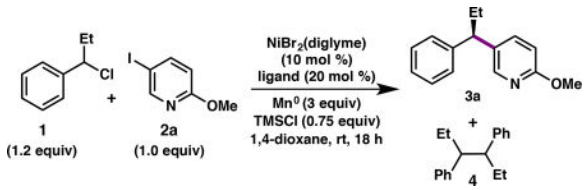
Table 1

Optimization of reaction conditions.[a]



Entry[a]	Ligand	Deviation from Standard Conditions	Yield 3a (%)[b]	Yield 4 (%)[b]	ee 3a (%)[c]
1	L1	None	84	8	90
2	L2	--	22	30	68
3	L3	--	64	21	75
4	L4	--	74	20	80
5	L5	--	4	0	60
6	L6	--	31	9	86
7	L1	Zn^0 instead of Mn^0	0	26	--
8	L1	TDAE instead of Mn^0	3	0	66
9	L1	TFA instead of TMSCl	0	25	--
10	L1	DMA instead of dioxane	14	13	67
11	L1	**5** instead of **2a**	72	24	89
12	L1	**6** instead of **1**	8	37	81

[a]Reactions conducted under N_2 on 0.05 mmol scale for 18 h.

[b]Determined by ^1H NMR versus an internal standard.

[c]Determined by SFC using chiral stationary phase.

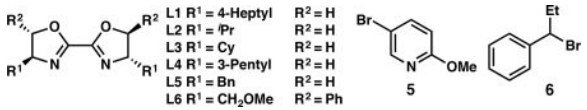
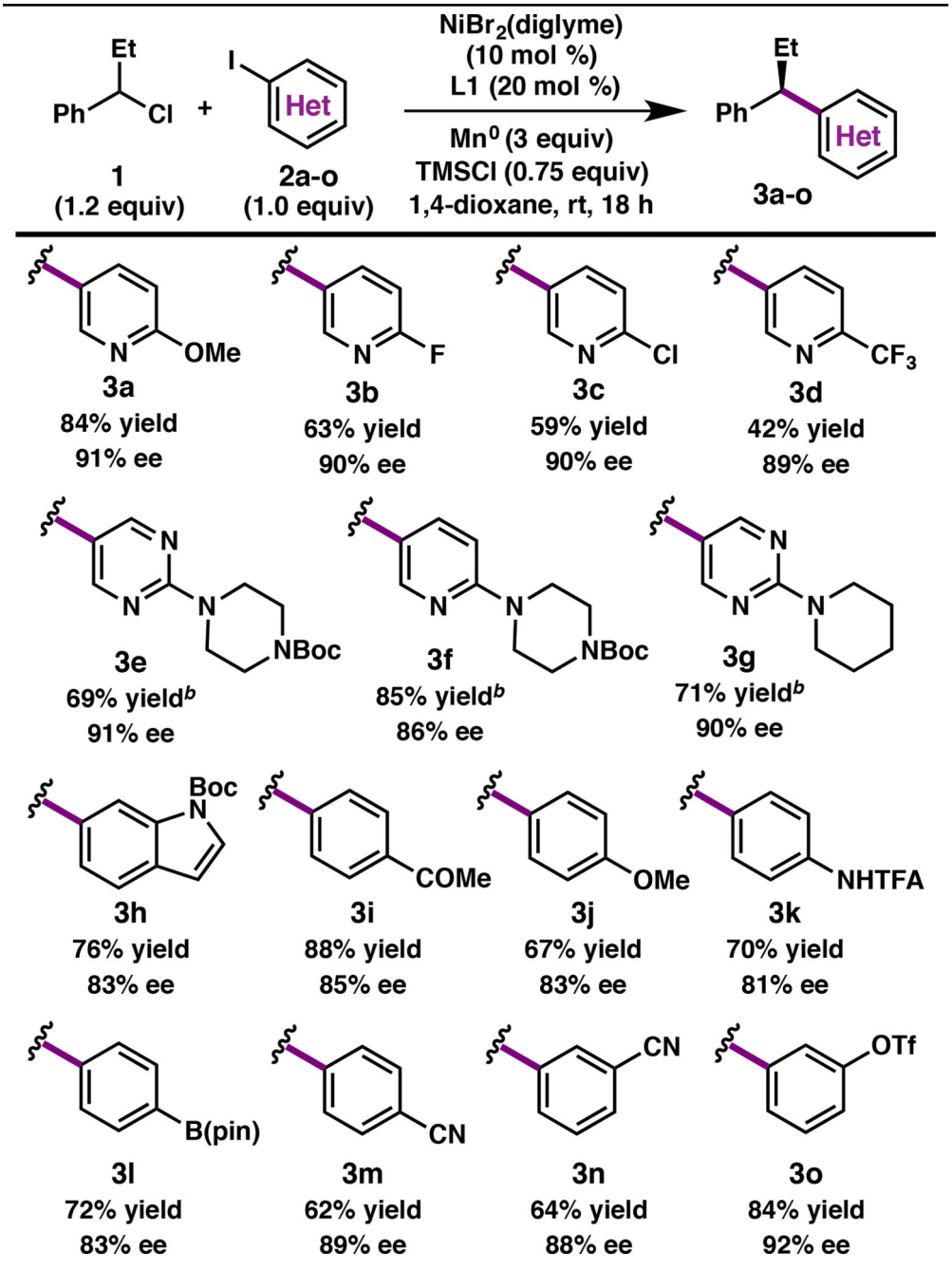


Table 2

Scope of (hetero)aryl iodides.[a]

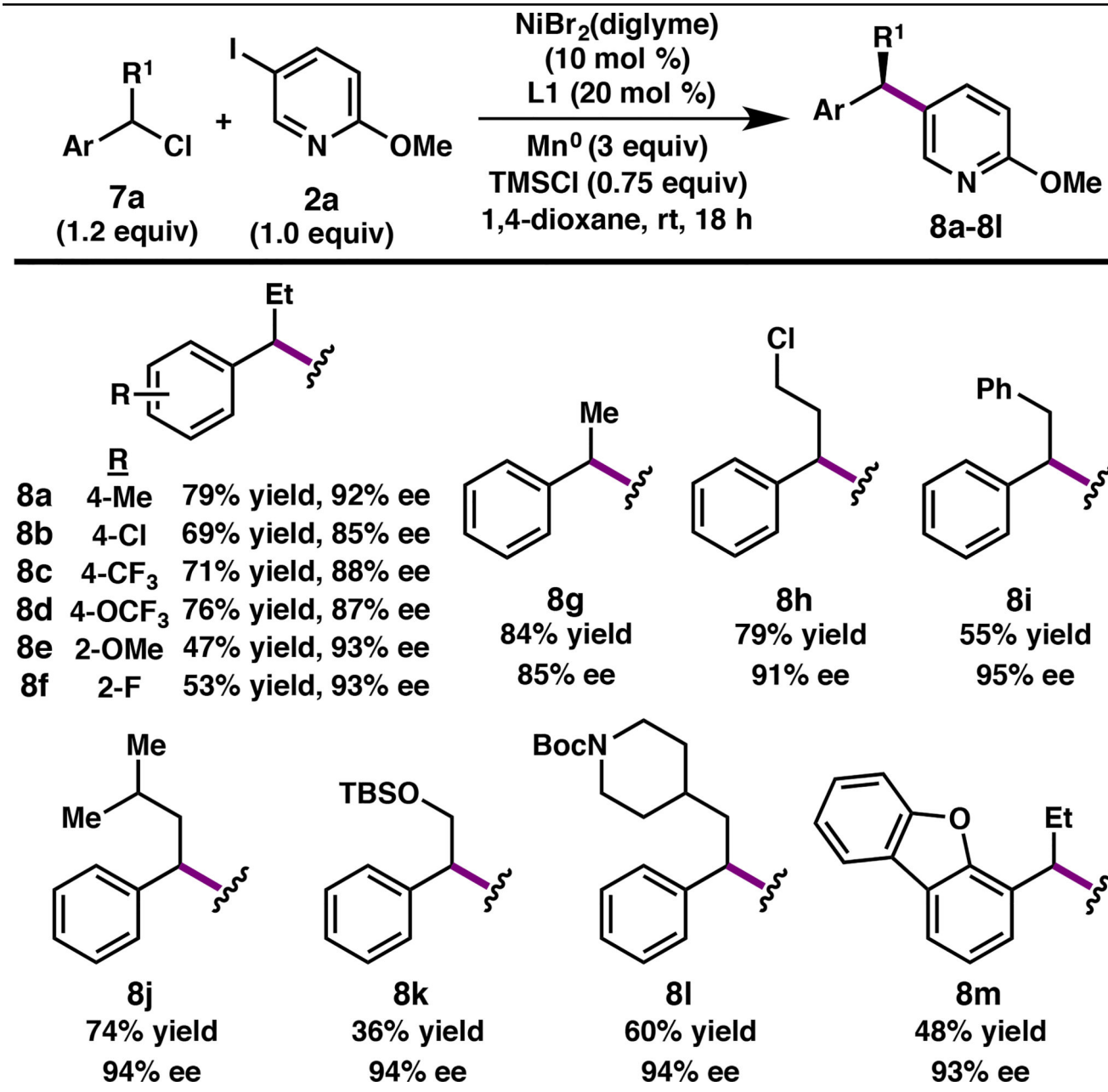


[a]Reactions conducted on 0.2 mmol scale. Isolated yields; ee is determined by SFC using chiral stationary phase.

[b]2.4 equiv of **1** is used.

Table 3

Scope of benzylic chlorides.[a]



[a]Reactions conducted on 0.2 mmol scale. Isolated yields; ee is determined by SFC using chiral stationary phase.